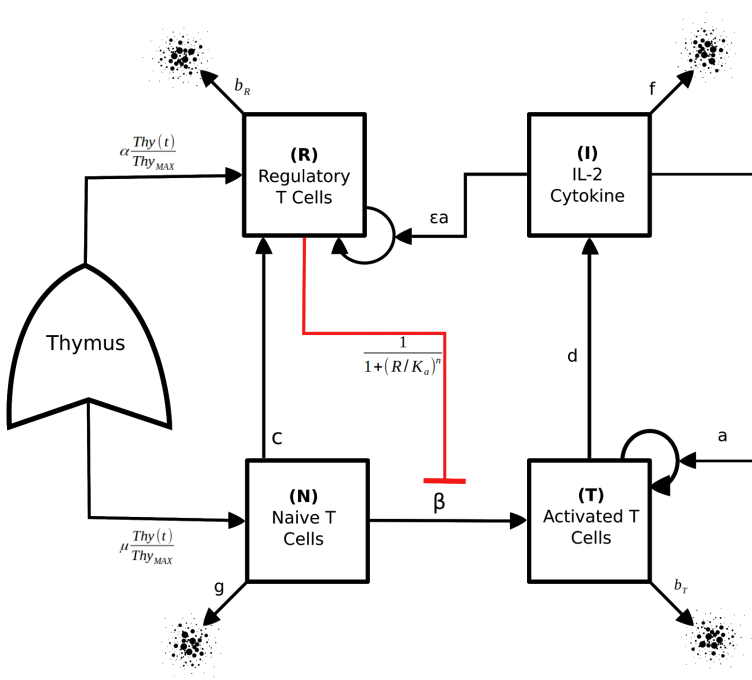
Coding Write Ups

How to use this document

At the beginning of each entry there will be an ‘Entry Number’. This number is associated with the parameter set found in the file *Parameter.csv*. Usually, this number represents the new parameter sets that I found and it is explained within the entry.

The first page is general information about the model

Diagram and Equations



$$\frac{dN}{dt} = \mu \frac{Thy(t)}{Thy_{max}} - \beta N \left(\frac{1}{1+(R/k_A)^n} \right) - cN - gN$$

$$\frac{dT}{dt} = \beta N \left(\frac{1}{1+(R/k_A)^n} \right) + aIT - b_T T$$

$$\frac{dR}{dt} = \alpha \frac{Thy(t)}{Thy_{MAX}} + \epsilon aIR + cN - b_R R$$

$$\frac{dI}{dt} = dT - e_T IT - e_R IR - fI$$

Parameter definitions

Below are the parameter definitions

<u>Thymus</u>

- **Alpha (α)** - T regulatory cells production rate
- **Mu (μ)** - Naive T cell production rate
- **Thy(t)** - Size of the thymus that grows through time. Using logistic equation, see entry below
- **Thy_max** - Maximum size of the thymus

<u>Naive T Cell Differentiation Rate</u>

- **C** = To T regulatory cells
- **Beta (β)** - To activated T cells

<u>T regulatory Cells</u>

- **Epsilon (ϵ) -** T regulatory cell self replication
- **z** - Strength of suppression on Naive T cell differentiation to activation
- **n** - Hill coefficient
- **kA -** half saturation rate

<u>IL-2 Cytokine Expression and Consumption</u>

- **d** - T cell expression rate
- **a** - IL-2 dependent activated T cell self replication rate
- **e_T** - Activated T cell consumption rate
- **e_R** - T reg consumption rate

<u>Death Rates</u>

- **g** - Naive T cells
- **b_T** - Activated T cells
- **b_R** - Regulatory T cells
- **f** - IL-2 Cytokine

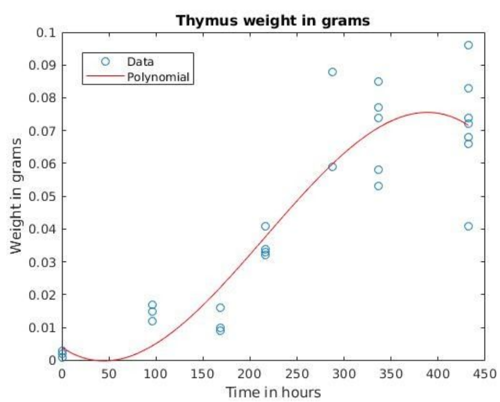
Experiments

Third Degree Polynomial

Purpose
I needed an equation that can emulate the growth of the thymus as a control swith for the thy/thy_max part of the equation. The goal is to have an equation that increase the growth rate of naive and Treg populations as time goes on.

What I did
I fit a 3rd degree polynomial to the data

Observation



Out of all types of polynomials that could fit this data, a 3rd degree polynomial was the best fit.

Conclusion
The 3rd degree polynomial was a bad fit. Only because the behaviors seen does not represent what is believed to be an appropriate behavior seen in biology. The dip at hour 50 and 375-ish is not what actually goes on. A much higher timeframe is likely to create weird behaviors of the model

Logistic Equation

Purpose

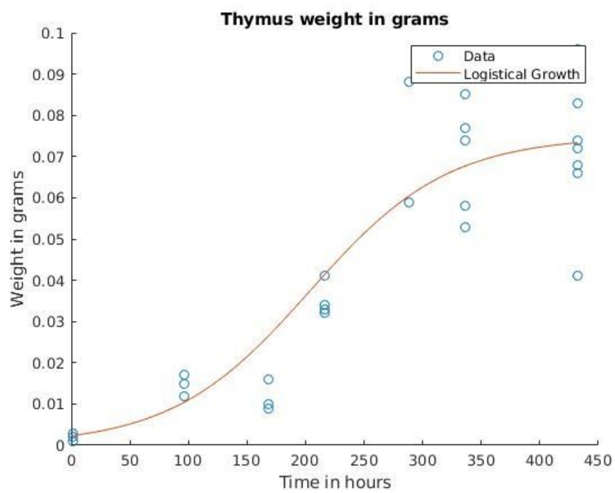
I needed another equation to fit to the thymus data, because the logistic equation does not make sense.

What I did

$$\frac{dm}{dt} = \lambda m\left(1 - \frac{m}{K}\right)$$

I fit the data to the equation to the left by using the least r squared method. An interesting thing happened as I was trying to find the right parameters; I couldn't set up the optimization algorithm to search for both the lambda and k parameters.

Observation



The logistic equation has a better fit to the data. There are no obvious signs that this equation won't work.

Conclusion

Below are the appropriate parameters and their values

- λ - 0.016932
- K - 0.074896

The logistic equation is a good fit to the model, with an r squared value of 0.0041752.

ASSUMPTION and final thought

Although this equation is a good fit for the data that I have and within the time frame given, it won't be a good fit for the future of the system. The thymus continues to grow past this time point and the way this equation is set up, it will not grow past its final size dictated by the K value. Luckily, we are not looking past this time point, for now.

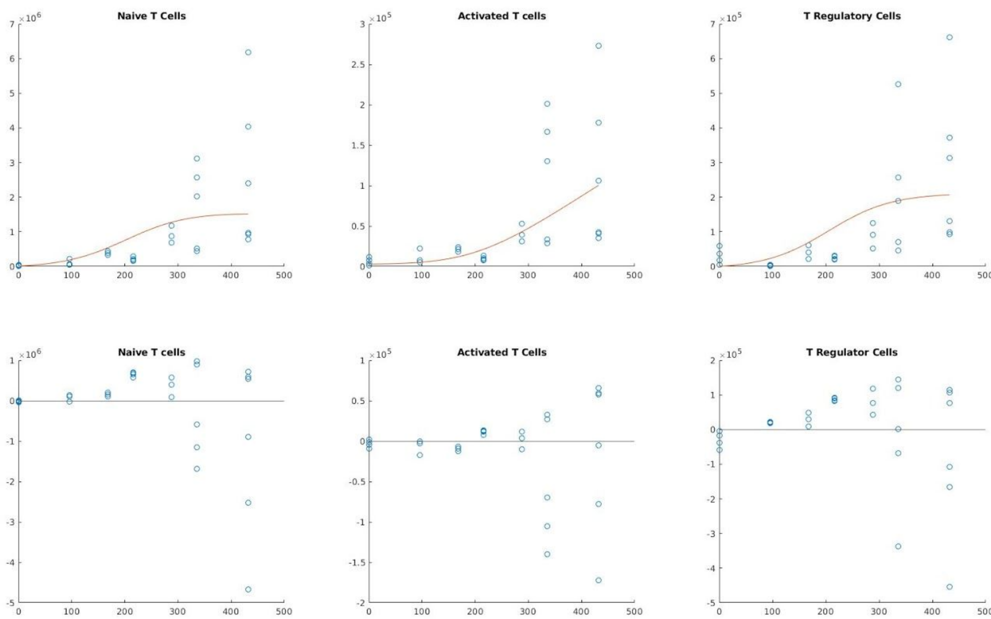
Entry Number: 16

Quick Summary
I added the logistic equation to control the growth of naive and tregs, then I tried to fit the alpha and mu parameters to the naive and treg data.

Background
Currently, we have found the right parameters for the logistic equation to establish the control switch for the thy/thy_max piece of my equation. The thy_max value will be 0.074896, the same value as the K value in the logistic equation. The logistic equation will be placed on the numerator (Thy), and will grow in value as the entire simulation goes forward in time.

Purpose
Now that I have an equation that I could use to control the growth of Naive and T regulatory cells. Now to fit alpha and mu parameters to the data with the new control switch in place.

Observation



Top layer is the data data with the model results that are the best fit. Below are the results of the optimization process

- **Alpha** - 217911.8588
- **Mu** - 1688320.5358

- **Rsquare -** 39221292357883.27

ASSUMPTION

At this point I have not touched the death rate of naive and treg cells, but I did estimate the values of their death rates before and kept it the same for this experiment. From a previous experiment, the death rates of these two populations were essentially 0.

Conclusion

It looks like a decent fit, there are no weird behaviors from what my eyes can see, the next step will be to calculate the death rate of naive and Treg cells.

List of Rates from data

Parameters	Information	Value	Stain
α	Rate of Treg from thymus	15.93452 x 10^3 / day 664 cells/ hr 66 cells / hr (10% contribution)	[Foxp3+]
μ	Rate of naive from thymus	298.2543 x 10^3 / day 12427 cells / hr	[CD4+] - [CD4+CD69+]
Thy	Thymus weight as it ages	4.375 milligrams / day 182 micrograms / hr	N/A
Thy_{max}	Maximum weight of thymus	96 milligrams	N/A
β	Rate of Naive to Activated T Cells	6.937961 x 10^3 / day 289 cells/ hr	[CD4+CD69+]
c	Rate of Naive to Tregs	90% contribution 598 cells / hr (90% contribution)	(1)
ε	Treg IL-2 dependent self replication	6.112009 x 10^3 / day 255 cells/ hr Keeps Treg replication relative to Act T 255 cells for each 8,000 IL-2 molecules / hr ε = 0.0328 ε*a*I*T	[Foxp3+KI67+]
K_A	Half rate parameter of suppression	Needs to be estimated	N/A
n	Hill coefficient	Needs to be estimated	N/A
d	IL-2 expression rate	1,000 molecules/cell−1h−1 100 unit/ml max per minute	(2) (3)
e_T	IL-2 consumption rate by activated T cells	3,000 molecules/cell−1h−1 100 unit/ml max per minute	(2) (3)
e_R	IL-2 consumption rate by Tregs	8,000 molecules/cell−1h−1	(2)
a	Activated T cell IL-2 dependent self replication	26.45375 x 10^3 / day 1102 cells / hr 1102 cells for each 1,000 IL-2 molecules / hr a = 1.102 a*I*T	[CD4+CD69+KI67+]
g	Naive T cell death rate	1.197 x 10^3 / day 126 cells / hr	([CD4+] - [CD4+CD69+) - [CD4+FC506+]
b_T	Activated T cell death rate	Needs to be estimated 1.197 x 10^3 / day (Naive) 126 cells / hr (Naive)	[CD4+CD69+KI67+FV506+]
b_R	Treg death rate	0.284 x 10^3 / day 55 cells / hr	[Foxp3+] - [Foxp3+FV506+]
f	Rate of constant extracellular IL-2 degradation	0.1/ h Halve life - 3.7 min	(2) (4)

1. Milanez-Almeida, Pedro, et al. "Foxp3+ regulatory T-cell homeostasis quantitatively differs in murine peripheral lymph nodes and spleen." *European journal of immunology* 45.1 (2015): 153-166.
2. Busse, Dorothea, et al. "Competing feedback loops shape IL-2 signaling between helper and regulatory T lymphocytes in cellular microenvironments." *Proceedings of the National Academy of Sciences* 107.7 (2010): 3058-3063.
3. Burger, Carol J., Klaus D. Elgert, and William L. Farrar. "Interleukin 2 (IL-2) activity during tumor growth: IL-2 production kinetics, absorption of and responses to exogenous IL-2." *Cellular immunology* 84.2 (1984): 228-239.
4. Donohue, John H., and Steven A. Rosenberg. "The fate of interleukin-2 after in vivo administration." *The Journal of Immunology* 130.5 (1983): 2203-2208.
5. Thornton, Angela M., et al. "Expression of Helios, an Ikaros transcription factor family member, differentiates thymic-derived from peripherally induced Foxp3+ T regulatory cells." *The Journal of Immunology* 184.7 (2010): 3433-3441.
6. Höfer, Thomas, Oleg Krichevsky, and Grégoire Altan-Bonnet. "Competition for IL-2 between regulatory and effector T cells to chisel immune responses." *Frontiers in immunology* 3 (2012): 268.